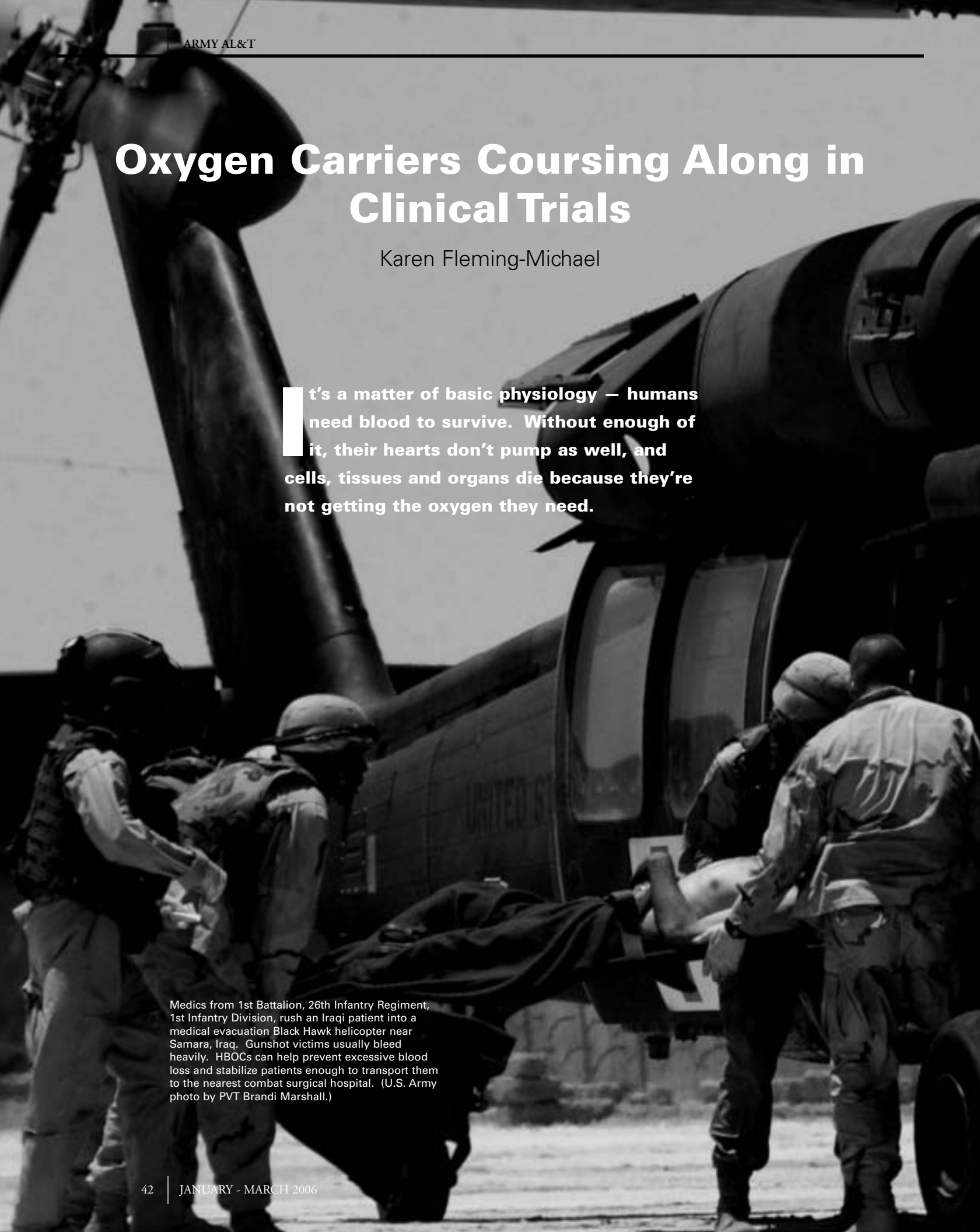
Oxygen Carriers Coursing Along in Clinical Trials

Karen Fleming-Michael

It's a matter of basic physiology — humans need blood to survive. Without enough of it, their hearts don't pump as well, and cells, tissues and organs die because they're not getting the oxygen they need.



Medics from 1st Battalion, 26th Infantry Regiment, 1st Infantry Division, rush an Iraqi patient into a medical evacuation Black Hawk helicopter near Samara, Iraq. Gunshot victims usually bleed heavily. HBOCs can help prevent excessive blood loss and stabilize patients enough to transport them to the nearest combat surgical hospital. (U.S. Army photo by PVT Brandi Marshall.)

When warfighters are bleeding severely on the battlefield, getting blood to them is tricky because blood requires refrigeration and has an extremely short shelf life. With this in mind, researchers have spent decades developing fluids called hemoglobin-based oxygen carriers (HBOCs) that do the blood's job of carrying oxygen to our tissues and organs.

"No oxygen equals cell death, tissue death," said COL Robert Vandre, U.S. Army Combat Casualty Care Research Program. "Once you get below a certain level of red cells in the blood, even if you can put in volume with intravenous fluids, you're not going to have enough oxygen and everything starts shutting down. The patient starts having inflammation problems and going into shock. Then everything falls apart."

To prevent that from happening, medical professionals' first choice for replacing lost blood will always be fresh, whole blood.

"The nice things about red cells, they not only carry oxygen, they also help in clotting blood," Vandre explained. "If you look at a blood clot, it's red. That's because it's made up of red cells that act like little sandbags. Platelets, thrombin and fibrinogen are the glue that hold all the red cells together."

HBOCs

"When red cells or whole blood just aren't available, an HBOC serves as a bridge until real blood is available," explained Dr. Michael Dubick, a senior research pharmacologist who manages resuscitation research at the U.S. Army Institute of Surgical Research. "An HBOC, though an oxygen carrier, is not a blood replacement. HBOCs don't do all the things that blood does and they don't offer the clotting benefits present in platelets," Dubick continued. "But they buy you time until you can actually get a blood transfusion."

"Anyone can receive an HBOC because everyone has hemoglobin," Vandre remarked. "The fluid doesn't have to be typed and cross matched like blood and doesn't require a full-blown blood donation program like the kind found in a hospital."

"HBOCs may also help when wounded warfighters face long evacuation times," Dubick suggested. "In Afghanistan, at times evacuation times were long. We've heard reports that they were from 12 to 36 hours. I think there was an anecdote of a helicopter being shot down at 14,000 feet, and it took time to get the people evacuated because they were still under

fire. If you have longer evacuation times, perhaps the regular fluid the medics were carrying wouldn't be good enough. You don't have blood, but you do want to give them something like blood as soon as possible."

The Army invented the first HBOC at the since-shuttered Letterman Army Institute of Research. "They first tried taking the hemoglobin out of the blood and used it to deliver oxygen, but straight hemoglobin is a bad idea," Vandre stated. "It's so small that it leaked out of the blood vessels quickly. Not only did it not do the oxygen-carrying job, it leached out and made the skin turn color."

"Once they linked hemoglobin molecules in big clumps, researchers moved past the leaking, but first-generation HBOCs had other problems. They raised the recipient's blood pressure, failing in clinical trials in Europe, where nearly three times as many patients in the treatment group died compared to the control group," Dubick recounted.

"No product has yet fully met the military's ideal of having a 2-year shelf life, needing no refrigeration and having no limit on the number of units that can be given. However, today's second-generation HBOCs in clinical trials are faring much better than their predecessors," Vandre pointed out.

"The grape-juice-colored fluids are packaged in a bag similar to red blood cells so they don't weigh too much. There's little chance of allergic reactions because everyone has hemoglobin, which makes blood red. They do seem to cause the skin to turn yellow as the liver processes the HBOC, but that's a temporary side effect," explained Dubick.

SPC Jennifer Neil, an Army medic with the 155th Brigade Combat Team, tends a patient who is suffering from dehydration at a civilian hospital in Iskandaryiah, Iraq, Nov. 26, 2005. (U.S. Marine Corps photo by LCPL Michael J. O'Brien.)

One HBOC, called PolyHeme, is already in clinical trials nationwide at trauma centers. In July 2005, Brooke Army Medical Center (BAMC) began participating in the trial after getting permission from the Secretary of the Army. "The Army is participating in this trial because we need an HBOC in the pre-hospital arena on the battlefield, and we need to be involved in the development of the product so when the product is delivered, we know and understand and are the experts on this product," said COL Toney Baskin, a trauma surgeon and principal investigator for the trial at BAMC, Fort Sam Houston, TX.

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"Getting permission from the Army was one hurdle for the trial. Getting community consent was another. A trauma patient doesn't know in advance that he's going to be a trauma patient," Vandre said. "And the ones that need red cells or HBOCs are the ones that are really badly hurt. You can't get informed consent from them to use an investigational new drug … and sometimes you can't get immediate consent from the next of kin, so you have to get consent of the community."

To gain community consent, officials at BAMC explained the trial to the military community and some of the outlying areas that Brooke services. "I think 87 percent of the people who attended said that they agreed with the study and approved the study," Dubick said. "On a personal basis, whether they would want to have the product themselves is another question." Organizers distributed bracelets for people to wear if they did not want to receive the product.

"The BMAC portion of the trial is still ongoing, with a goal of enrolling 20 patients who are 18 or older, not pregnant and who have a systolic blood pressure (the number on top) less than 90," remarked Baskin, who serves as

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Chief of Trauma and Critical Care, Trauma Division, U.S. Army Institute of Surgical Research and BAMC.

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Microbubbles

Another potential oxygen carrier still in early developmental stages is microbubbles. Instead of using hemoglobin, the microbubbles are fluorocarbons, specifically dodecafluoropentane, a cousin of Freon, the automobile air conditioning fluid. The solution is liquid at room temperature, but turns into bubbles when placed in the body.

"When the bubbles go to the lungs, they … will actually suck in oxygen from your lungs and when they get out to the tissues, they'll give off the oxygen," Vandre remarked. "They act much like an HBOC.

"Studies using the microbubbles in a laboratory setting show that three tablespoons carry as much oxygen as an average person's blood. Packaged as a liquid in a tiny vial, microbubbles appear to be very safe," said Vandre. "They are used in such a low volume that a medic could carry them easily.

"If somebody was losing a lot of blood, the first thing to do is try to stop the bleeding, then give Hextend (a resuscitation fluid) to keep the volume up," Vandre explained. "If they're still not doing well because they lost too many red cells, then you'd give them this — if red cells weren't available. Such a small amount can make such a big difference."

Currently, Vandre's program is evaluating 16 resuscitation products to find the best candidates to take to clinical trial. If microbubbles win, they could enter clinical trials by 2008. Regardless of which product wins, the experts seem to agree that oxygen can make the difference between life and death in trauma cases.

"I have been in situations where patients have been losing blood, and blood was not available," Baskin recounted. "Had there been an HBOC available, perhaps lives could have been saved."

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